

Report Title: Acute Dermal Toxicity Study in Rabbits

Test Type: Acute Dermal Toxicity

Conducting Laboratory and Location: International Research and Development Corporation

Test Substance(s): #T-7119 -2% Octopirox in shampoo at pH 7.5

Species: Rabbit

of Animals: 3 male, 3 female

Test Conditions: 3 male and 3 female New Zealand White Rabbits exposed to 2000 mg/kg on abraded skin for 24 hours. Rabbits were observed for 14 days.

Results: Minimum lethal dermal dose in both male and female rabbits was >2.0 g/kg.

Study #: 191-080; see related studies 191-081 and 191-082

Report Date: 11/09/77

Accession #: 19194

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Acute Dermal Toxicity Study in Rabbits

SPONSOR: Procter and Gamble Company

TEST MATERIAL: T-7119

STUDY NUMBER: 191-080

DATE: November 9, 1977

PROCEDURE: Animals

Six New Zealand White rabbits (obtained from Kuiper's Rabbit Ranch, Gary, Indiana), equally divided as to sex, weighing 2396 to 2703 grams, were used in this study. They were maintained in accordance with the recommendations contained in H.E.W. Publication No. 74-23 (N.I.H.) entitled "Guide for the Care and Use of Laboratory Animals" and were conditioned for a minimum of 12 days prior to study initiation.

Administration

The hair was clipped from the back of each rabbit. The skin was abraded for one male and two females. The test material was applied to the back as received at a dosage level of 2000 mg/kg. The application site was then covered with gauze bandaging, rubber dam and several wrappings of Elastoplast tape. A collar was also applied. Following the 24 hour application period, the collars and wrappings were removed and any remaining test material was removed with a wet disposable paper towel.

Observations

The rabbits were observed for pharmacotoxic signs, dermal irritation and mortality at 24 hours and daily thereafter for a total of 14 days. All animals which died on study were subjected to gross necropsy examination as were all survivors at 14 days. (See attached protocol for specific experimental design used.)

191-080

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Acute Dermal Toxicity (cont.)

RESULTS:

Dose - Mortality Data

Dosage Level mg/kg	Number of Deaths														Total Mortalities			
	Hrs.	Days																
	0-4	1	2	3	4	5	6	7-14										
	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	Male	Female	Total			
2000															0/3	0/3	0/6	

The minimum lethal dermal dose of T-7119 in the male and female albino rabbit was found to be greater than 2000 mg/kg.

Pharmacotoxic Signs

The following pharmacotoxic signs were observed during the 14-day observation period:

Males

	Normal	Diarrhea	Urine Stained Abdomen	Soft Stool
Days 1-8	3/3			
Days 9-10	2/3	1/3		
Day 11	3/3			
Day 12	2/3	1/3		
Days 13-14	2/3		1/3	1/3

Acute Dermal Toxicity (cont.)

Females

Normal

Days 1-14 3/3

Dermal Irritation Signs

The following signs of dermal irritation were observed during the 14-day observation period: (See the page following.)

T-7119:

Dermal Irritation2000 mg/kg

	Erythema				Edema				Atonia				Desquamation					Coriaceousness				Fissuring				Eschar		Ex-foliation	
	None	Very Slight	Slight	Moderate	None	Very Slight	Slight	Moderate	None	Very Slight	Slight	Moderate	None	Very Slight	Slight	Moderate	Marked	None	Very Slight	Slight	Moderate	None	Very Slight	Slight	Moderate	No	Yes	No	Yes
Day 1		4/6	2/6		1/6	5/6			1/6	5/6			6/6					6/6				6/6				6/6			6/6
Day 2		3/6	3/6		1/6	1/6	4/6			2/6	4/6		6/6						6/6			3/6		3/6		6/6			6/6
Day 3		4/6	2/6		1/6	1/6	4/6			2/6	4/6		6/6						6/6			3/6	1/6	2/6		6/6			6/6
Day 4		3/6	3/6		1/6	1/6	4/6			4/6	2/6		6/6						5/6	1/6				6/6		6/6			6/6
Day 5		3/6	3/6		1/6		5/6			2/6	4/6		5/6	1/6					1/6	5/6				6/6		6/6			6/6
Day 6		6/6			1/6		5/6			1/6	5/6		5/6		1/6				1/6	5/6				6/6		6/6			6/6
Day 7		6/6			1/6	1/6	4/6			1/6	5/6		4/6	1/6	1/6				1/6	5/6				6/6		6/6			6/6
Day 8		6/6				2/6	4/6			3/6	3/6		3/6	1/6	1/6	1/6				6/6				2/6	4/6	6/6			6/6
Day 9		6/6				3/6	3/6			1/6	2/6	3/6	2/6	1/6	2/6	1/6				6/6				2/6	4/6	6/6			6/6
Day 10		6/6				4/6	2/6		1/6	1/6	2/6	2/6	1/6	2/6	2/6	1/6			4/6	2/6			1/6	3/6	2/6	6/6			6/6
Day 11		1/6	5/6		1/6	2/6	3/6		1/6	1/6	2/6	2/6	1/6		4/6	1/6			1/6	4/6	1/6		1/6	5/6		6/6			6/6
Day 12		1/6	5/6			4/6	2/6		1/6	1/6	2/6	2/6	1/6		4/6	1/6			1/6	4/6	1/6		1/6	5/6		6/6			6/6
Day 13		1/6	5/6		1/6	2/6	3/6		1/6	1/6	2/6	2/6	2/6				4/6		1/6	3/6	2/6	1/6		3/6	2/6	6/6			6/6
Day 14		2/6	4/6		2/6	4/6			1/6	2/6	3/6						6/6	1/6		2/6	3/6	6/6				6/6			6/6

Acute Dermal Toxicity (cont.)

RESULTS
(cont.):

Body Weights

The following body weights were obtained during the 14-day observation period:

<u>Individual Rabbit No.</u>	<u>Sex</u>	<u>Control Weight (grams)</u>	<u>7-Day Weight (grams)</u>	<u>14-Day Weight (grams)</u>
29481	Male	2597	2715	2695
29485	Male	2618	2390	2710
29487	Male	2396	2425	2503
29484	Female	2650	2725	2725
29486	Female	2703	2723	2935
29488	Female	2537	2373	2690

Necropsy Findings

The necropsy findings on the following page were obtained following the 14 days of the study period:

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Acute Dermal Toxicity (cont.)

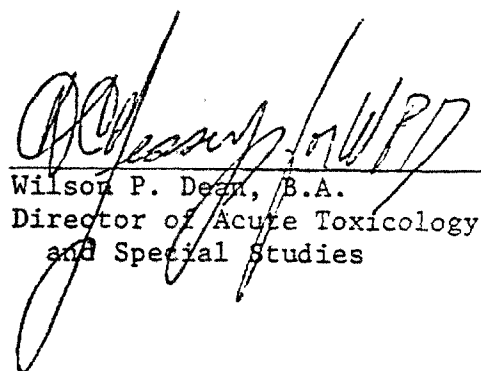
Gross Necropsy Observations:

Gross Necropsy Observations	Dosage Level (mg/kg)	
	2000	
	Male	Female
	Number Showing Sign/Number Necropsied	
Hair at application site yellow in color	3/3	2/3
Skin at compound application site thickened	2/3	1/3
Edema at application site	1/3	
Regional lymph nodes slightly enlarged	2/3	
Focal consolidation of lungs and cardiac lobes	1/3	
Distended urinary bladder	1/3	
Thickened urinary bladder	1/3	
Foci on mucosa of bladder; 3mm large	1/3	
Fluid around perineal area, rear legs and ventral abdomen	1/3	

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Acute Dermal Toxicity (cont.)



Wilson P. Dean, B.A.
Director of Acute Toxicology
and Special Studies

Approved by: D. Clifford Jessup, Ph.D.
Associate Director of Research

Date: November 9, 1977

Lab Project No. 191-080 Sheet 1 Date 8/5/77 Authorized by Dr. Jessup

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Compound	Identification Number	IRDC No.
T-7119		A-325

TITLE: ACUTE TOXICITY STUDIES IN RATS AND RABBITS

Conduct in accordance with the attached protocol.

Acute Percutaneous Toxicity - Rabbit

Date:

Issue #2

Purpose: To determine whether a substance is toxic when absorbed through the skin; to permit estimation of the degree of irritancy of a substance.

Animals: Rabbits, New Zealand albinos, three male and three female per test group, 2200-3000 grams.

Dosage Levels: Use 2 grams of test material per kilogram body weight.

Procedure: An area on the back of each animal approximately 25% of the total body surface is clipped with an Oster small animal clipper. The skin of three animals (two males and one female) is left intact, and the skin of the other three is abraded with a clipper head so as to penetrate the horny layer of the epidermis without causing bleeding.

Spread the test material evenly within the clipped area. Cover with a layer of 8-ply gauze, rubber dam and several wrappings of 75 mm Elastoplast tape. Dry or powdered materials are placed directly onto the gauze, which is spread over a layer of rubber dam and Elastoplast tape. Place the animal on his back over the test material and secure the Elastoplast tape around the trunk. Moistening of dry or powdered materials is optional. If this is done, record the amount and type of moisture added. Put the animals in Newmann (1) harnesses to prevent their removing the wrappings. After 24 hours, uncover the test sites, remove the test material with a wet disposable paper towel and evaluate the skin irritation following the attached scale. Record daily observations for the next two weeks. Necropsy and examine grossly all animals that succumb. On the 14th day, count, weigh, and necropsy the surviving animals.

(1) Newmann, E. A. (1963) Lab. Animal Care, 13, 207-210.

APCT Acute Percutaneous Toxicity - Rabbit (cont'd)

Report:

Individual animal observations including deaths, if any, degree of skin irritation as a function of time, body weights, signs of gross systemic effects and necropsy observations are reported.

Principal Investigator: M. J. Winrow

Date: 7/28/77

EVALUATION OF SKIN REACTIONS (CODE)

Erythema

- 0 - None
- 1 - Slight (barely perceptible)
- 2 - Moderate (well defined)
- 3 - Severe (beet red)

Edema

- 0 - None
- 1 - Slight (barely perceptible to well defined by definite raising)
- 2 - Moderate (raised approximately 1 mm)
- 3 - Severe (raised more than 1 mm)

Atonia (not including eschar area)

- 0 - Normal
- 1 - Slight (slight impairment of elasticity)
- 2 - Moderate (slow return to normal)
- 3 - Marked (no elasticity)

Desquamation (not including eschar area)

- 0 - None
- 1 - Slight (slight scaling)
- 2 - Moderate (scabs and flakes)
- 3 - Marked (pronounced flaking with denuded areas)

Fissuring

- 0 - None
- 1 - Slight (definite cracks in epidermis)
- 2 - Moderate (cracks in dermis)
- 3 - Marked (cracks with bleeding)

Eschar

- N - No
- Y - Yes

Exfoliation (sloughing of the eschar tissue)

- N - No
- Y - Yes